Original Article

The role of the female gender on mid-term outcome after coronary artery bypass grafting: a retrospective study

Paolo Nardi[1], Calogera Pisano[1], Carlo Bassano[1], Fabio Bertoldo[1], Dario Buioni[1], Vincenzo Labriola[1], Alessandro Cristian Salvati[1], Mattia Scognamiglio[1], Claudia Altieri[2], Giovanni Ruvolo[1]

[1]Cardiac Surgery Division, Tor Vergata University Hospital, Rome, Italy; [2]Unit of Cardiology of the Cardiac Surgery Division, Tor Vergata University Hospital, Rome, Italy

Contributions: (I) Conception and design: P Nardi; (II) Administrative support: C Altieri, G Ruvolo; (III) Provision of study materials or patients: C Pisano, C Bassano, F Bertoldo, D Buioni, AC Salvati, M Scognamiglio, V Labriola; (IV) Collection and assembly of data: P Nardi; (V) Data analysis and interpretation: P Nardi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prof. Paolo Nardi, MD, PhD. Cardiac Surgery Division, Tor Vergata University Hospital, Viale Oxford 81, PC 00133, Rome, Italy. Email: pa.nardi4@libero.it.

Background: Data on female gender differences on clinical prognosis after coronary artery bypass grafting (CABG) are still controversial. We evaluated retrospectively the impact of women patients in comparison with men undergoing CABG on mid-term outcome.

Methods: Between December 2014 and March 2022, 1,044 consecutive patients (162 females, 15.5%, 882 males, 84.5%) underwent isolated CABG. The mean follow-up was 40±27 (median 38) months. Logistic and Cox model analysis regressions were used to assess the risk of female gender and other variables, Kaplan-Meier estimates to assess survival rates.

Results: Women did not have a significant higher operative mortality than men (3.09% *vs.* 1.93%; P=0.37). There was no difference in the use of left internal mammary artery (97.5% *vs.* 94.9%; P=0.85). Independent predictors of early mortality were emergency CABG (P<0.0001), percutaneous coronary intervention (PCI) within 30 days (P=0.0026), and higher EuroSCORE II (P=0.0155). At 7.5 years, actuarial survival was 87%±3.6% for female gender *vs.* 88%±1.9% in male gender (P=0.41), freedom from cardiac death 97%±1.8% *vs.* 96.6%±1.0% (P=0.6), freedom from major adverse cardiac events (MACE) 87%±6.2% *vs.* 89.7%±2.5% (P=0.96). Independent predictor of all-causes death and cardiac death was the advanced age (74 years in dead patients *vs.* 67 years in survivors) (P<0.0001). Female gender was not a predictor of either operative mortality (P=0.34) or worse mid-term outcome (P=0.41).

Conclusions: Women undergoing CABG with the same surgical techniques currently adopted for men, do not appear to be associated with worse early prognosis. Freedom from late all-causes mortality, cardiac death and adverse cardiac events are comparable and equally satisfactory, highlighting the positive protective effect of CABG over time also in women.

Keywords: Gender; women health; coronary artery bypass grafting (CABG)

Submitted Jun 12, 2023. Accepted for publication Nov 03, 2023. Published online Feb 04, 2024.
doi: 10.21037/jtd-23-932
View this article at: https://dx.doi.org/10.21037/jtd-23-932

Introduction

Background

Coronary artery bypass grafting (CABG) surgery remains currently the most appropriate used strategy of myocardial revascularization in patients affected by complex or multivessel coronary artery disease. Indeed, despite in the last 20 years clinical profile of the patients undergoing surgery has progressively worsened, presenting older age and greater number of associated comorbidity, i.e.,

peripheral vascular disease, chronic renal dysfunction, obstructive pulmonary disease, thanks to surgical and anesthetic improvements, in most centers performing routinely CABG, operative mortality continues to be contained at 2–3%.

Rationale and knowledge gap

In Western countries in the last 15 years, the incidence of women among patients operated on has been steadily increasing, and several retrospective studies with larger series of female patients have compared surgical their outcomes with males, in order to understand whether women and men benefit equally from CABG surgery. Numerous analyses have shown that female gender appears to be at a significantly higher risk of operative mortality, with a reported mortality at least 2–3 times higher than in males (1-6). Just recently, in a cohort study of over 1 million CABG patients operated on in the US, it has been observed that women undergoing CABG in comparison with men continue to have a higher operative mortality, i.e., approximately double (2.8% *vs.* 1.7%), and a greater morbidity (22.9% *vs.* 16.7%) (7). Several variables have been examined to explain the worse perioperative outcomes in female gender and therefore identified as predictors: the advanced age, the higher incidence of cardiovascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia, obesity); the clinical-anatomic characteristics of ischemic heart disease typically present in women on admission, i.e., the reduced caliber of coronaries associated to lower body surface area. Other studies have also shown a significantly reduced long-term survival and a lower freedom from adverse cardiovascular events in female gender compared to the male counterpart. The main controversial aspect remains if the differences in early and late outcome are due to different risk profile between men and women undergoing CABG or if female gender "*per se*" is an independent risk factor of worse prognosis, even after CABG (6-9). On the other hand, fewer studies have reported no differences in clinical outcomes after CABG based on gender analysis.

Highlight box

Key findings

- We evaluated retrospectively the impact of female gender in comparison with male one undergoing coronary artery bypass grafting (CABG) on the mid-term outcome.

What is known and what is new?

- Several retrospective studies have shown that female gender appears to be at higher risk of operative mortality, and that female gender "*per se*" is an independent risk factor of worse prognosis, even after CABG.
- From what was observed in our study, women undergoing CABG with the same surgical techniques and medical therapy currently adopted for male gender, do not appear to be associated with worse prognosis, highlighting the positive protective effect of CABG over time in both women and men.

What is the implication, and what should change now?

- It is therefore clear that it is necessary to offer the same diagnostic and therapeutic opportunities to the female gender as offered for the male sex.

Objective

Aim of our study was to retrospectively analyze the cohort of all consecutive females and males patients undergoing isolated CABG at our center, in order to evaluate the influence of female gender on early and long-term results, and analyze the potential different clinical presentation and risk profile gender-based. We have also investigated other several risk factors and predictors potentially influencing the short-term mortality and morbidity, and the mid-term outcome up to 7.5 years after surgery. Our a priori hypothesis is that women currently undergoing CABG can show the same satisfactory early and mid-term results with the surgical techniques of revascularization adopted for their male counterpart. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-932/rc).

Methods

From December 2014 to March 2022, at the Cardiac Surgery Division of the Tor Vergata University of Rome - Tor Vergata Polyclinic, 1,044 patients underwent an isolated intervention of CABG; 162 patients (15.5%) were females, 882 (84.5%) males. This patient population was the subject of our retrospective study.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Tor Vergata Polyclinic (108/23 No. Protocol code, date of approval 05.05.2023). Informed consent was obtained from all subjects involved in the study.

Clinical features

For both groups of patients' age, height, and weight were taken into account; the body mass index was evaluated with the Quetelet formula (weight/height^2). Clinical conditions were assessed at admission, i.e., the score risk of patient calculated by EuroSCORE II evaluation system for CABG (European System for Cardiac Operative Risk Evaluation), the presence of stable or unstable angina, myocardial infarction, the indication to surgery, i.e., elective, urgent, emergency CABG. In addition, the incidence of previous or recent preoperative myocardial infarction, i.e., within 30 days, and of previous percutaneous coronary revascularization, even performed within 30 days of CABG were assessed. The cardiovascular risk factors analyzed were diabetes mellitus, especially insulin-dependent diabetes, smoking, dyslipidemia, hypertension.

Associated pathologies

The following pathologies were considered: obesity, defined by a value of body mass index >30 kg/m^2; chronic obstructive pulmonary disease, expressed with a volume forced expiratory in 1 s; <75% of the normal value, or requiring bronchodilators. Arterial peripheral vascular disease was considered to be significant in presence of claudication with autonomy walking <200 meters and pulses hypo-sphygmia; carotid artery disease in presence of stenosis >50% detected at the ultrasound echo-color Doppler. Chronic renal dysfunction was defined as moderate in presence of creatinine clearance 50–80 mL/min, severe with creatinine clearance <50 mL/min. Thyroid dysfunction, i.e., hyper- or hypothyroidism was considered on the basis of the clinical history and need for hormone substitute therapy, and was reassessed on admission by the measurements of serum level of FT3, FT4, thyroid stimulating hormone (TSH) hormones.

Anatomical and hemodynamic data

The extent of the coronary artery pathology was assessed on the basis of coronary angiography, performed in all patients. The caliber of the coronary arteries bypassed was measured intraoperatively with calibrated 1.0, 1.5 and 2.0 mm probes. The type of coronary disease, i.e., diffuse atherosclerotic disease with plaques, predominantly calcific and fibrotic disease of the coronary wall was evaluated on the operative field. The left ventricular (LV) function, expressed as LV ejection fraction, was evaluated by preoperative transthoracic and intraoperative trans-esophageal echocardiography in all cases.

Surgical strategies

Beating-heart coronary artery bypass surgery was not performed in presence of LV ejection fraction less than 30%, LV end-diastolic diameter greater than 60 mm, distal diffuse narrowing of coronary arteries, intra-myocardial course of the left anterior descending (LAD) coronary artery, surgery required in presence of perioperative hemodynamic instability, and availability of the devices required for off-pump surgery. To perform off-pump CABG, in all cases it was required perfusionist's stand-by on a ready-dry state (i.e., mounted, non-primed cardiopulmonary bypass circuit). In other cases, the decision to perform off- or on-pump CABG depended on the surgeon's choice.

Left internal mammary artery was used as graft to revascularize the LAD artery, in association with saphenous vein grafts for the revascularization of the right coronary artery and/or to the left circumflex artery branches. The use of the autologous saphenous vein alone without the internal mammary artery harvesting was reserved for patients suffering from severe pulmonary disease, i.e., in presence of diffuse bronchiectasis and emphysematous pathology, or of proximal stenosis of the subclavian artery, or when serious hemodynamic and or electrical instability was present at the anesthetic induction.

Definitions and data analysis

The current study considered all consecutive patients undergoing CABG as an isolated procedure. Other CABG procedures performed in association with heart valve repair or replacement, or in association with ascending aorta repair, were not included. The study was retrospective.

Operative or in-hospital mortality included deaths occurring in the hospital or within 30 days after CABG operation. The main cardiac and non-cardiac postoperative complications analyzed were perioperative myocardial infarction, defined as an increase of serum troponin I >20 ng/mL associated with the increase of creatine-kinase muscle-brain (CK-MB) enzyme greater than 10% of the total CK enzyme and the onset of electrocardiogram (ECG) anomalies. Low cardiac output syndrome was defined in presence of a cardiac index value lower than 2.0 L/min/m^2 with or without renal impairment requiring inotropic

support for a period greater than 48 hours, or when it needs intra-aortic balloon pump insertion.

Respiratory failure was defined as an episode of primary respiratory insufficiency requiring mechanical support for a period greater than 48 h, tracheal re-intubation, or intermittent application of non-invasive positive-pressure ventilation.

Follow-up evaluation

Follow-up was performed with an outpatient visit to the patient and/or by telephone interview at 40±27 (median 38, range, 3–94) months after CABG. The following adverse cardiac and cardiovascular events were evaluated over time: late death for all causes, cardiac death, and major adverse cardiac events (MACE) rate, defined as death from cardiac causes, myocardial infarction onset, and need for new myocardial revascularization. The follow-up ended in July–August 2022.

Statistical analysis

Statistical analysis was performed with the use of Stat View 4.5 (SAS Institute Inc., Abacus Concepts, Berkeley, CA, USA). Contingency tables raw data with the use of Chi-, G-Squared, and Fisher's exact tests for categorical variables and the unpaired Student's *t*-test for continuous variables, were calculated to perform the comparisons of females and males patients. A total of twenty-four variables were analyzed. Preoperative analyzed variables included age, gender, EuroSCORE II; clinical presentation, i.e., previous and recent myocardial infarction, stable angina or acute coronary artery syndromes, i.e., unstable angina, STEMI (electrocardiographic ST tract elevation myocardial infarction), NSTEMI (non-ST elevation myocardial infarction), LV ejection fraction; body mass index, obesity. Preoperative variables included also comorbidity, i.e., smoke, diabetes mellitus, hyperlipidemia, hypertension, chronic obstructive pulmonary disease, chronic renal dysfunction, thyroid dysfunction, carotid and peripheral vascular disease; indication to CABG, i.e., elective, urgent, or emergency, percutaneous coronary intervention (PCI) prior to CABG. The EuroSCORE was calculated as a continuous variable; on the basis of its value. Three groups of patients were then divided; those at low (L) risk with a EuroSCORE value between 0.5% and 3.0% (783 patients), those at medium (M) risk with a value between 3.1% and 6.0% (171 patients), and those at high (H) risk, with a value greater than 6.0% (90 patients).

Intraoperative variables included the number of grafts per-patient, cardiopulmonary bypass and aortic cross-clamp times, the use of internal mammary artery graft, the diameter of the coronary vessels and type of coronary disease evaluated on the operative field. Univariate analysis of preoperative and intraoperative variables considered as potential risk factors of operative mortality was performed; the variables that reached a P value <0.1 were included in the multivariate logistic regression analysis.

Five survival and event-free survival curves were calculated. Late survival, not including in-hospital mortality, freedom from late cardiac death and from MACE were calculated by means of the Kaplan-Meier method, and were expressed as mean values of percentage ±1 standard deviation. The Mantel-Cox Log-rank and Breslow-Gehan-Wilcoxon rank tests were used to compare the curves of freedom from events, i.e., among females and males, patients with and without a specific risk factor. The Cox proportional regression analysis was used to evaluate the influence of the calculated variables on time to death. All continuous values were expressed as mean ±1 standard deviation. A P value <0.05 indicated statistically significant differences.

Results

Clinical features and associated pathologies

As compared with men, at admission women had older age, higher EuroSCORE II, higher incidence of thyroid dysfunction, were shorter and weighed less, but they were more obese; males more frequently smoked (P<0.05, for all comparisons) (*Table 1*). Although with non-statistically or just borderline significant values, women presented with better LV systolic function and with higher incidence of hypercholesterolemia, while men with higher incidence of chronic pulmonary disease (*Table 1*).

Anatomical intraoperative data and perioperative results

The mean diameter of the coronaries (anterior descending artery 1.53 *vs.* 1.70 mm, P<0.0001; diagonal branch/s 1.41 *vs.* 1.61 mm; obtuse marginal branch/s 1.48 *vs.* 1.70 mm; right coronary artery 1.56 *vs.* 1.93 mm; descending posterior artery 1.32 *vs.* 1.49 mm) was consistently lower in women across all vessels (P<0.05, for all comparisons) (*Table 2*). Eighty-five CABG operations (8.1%) were off-

Table 1 Clinical preoperative characteristics and associated pathologies in women and males CABG patients

Characteristics	Women (n=162)	Men (n=882)	P value
Age, years	70.5±8.6	66.8±8.9	<0.0001
EuroSCORE II, %	3.23±2.15	2.63±2.38	0.04
Previous MI (>30 days)	32 [20]	180 [20.4]	0.54
Recent MI (≤30 days)	32 [20]	226 [25.6]	0.14
Left ventricular ejection fraction, %	54±8.4	52±8.8	0.05
Clinical presentation			0.11
Stable angina	52 [32]	347 [39.3]	
Unstable angina	55 [34]	302 [34.2]	
Non-STEMI	43 [26.5]	171 [19.4]	
STEMI	12 [7.4]	62 [7.0]	
Indication to CABG			0.59
Elective	36 [22.2]	204 [23]	
Urgent	121 [74.7]	662 [75]	
Emergency	5 [3]	16 [1.8]	
Previous PCI	18 [11.1]	113 [12.8]	0.46
Previous PCI <30 days	4 [2.5]	25 [2.8]	0.43
Diabetes mellitus	67 [41.4]	344 [39]	0.61
Diabetes mellitus insulin-depend	46 [28]	304 [34.5]	0.24
Hypertension	144 [89]	767 [87]	0.11
Hypercholesterolemia	123 [76]	598 [68]	0.08
Smoke	40 [25]	441 [50]	<0.0001
Thyroid dysfunction	8 [5]	2 [0.2]	<0.0001
Weight, kg	68.9±10.8	79.5±12.7	<0.0001
Height, m	1.62±5.9	1.71±6.4	<0.0001
Body mass index, kg/m^2	27.1±3.9	27.2±4.1	0.87
Obesity	45 [28]	158 [18]	0.006
Chronic pulmonary disease	7 [4.3]	69 [7.8]	0.06
Severe chronic renal dysfunction	12 [7.4]	81 [9.2]	0.59
Moderate chronic renal dysfunction	42 [26]	238 [27]	0.24
Carotid artery disease	22 [13.6]	101 [11.5]	0.20
Peripheral vascular disease	21 [13]	88 [10]	0.10

Data are presented as mean ± standard deviation or n [%]. CABG, coronary artery bypass grafting; MI, myocardial infarction; STEMI, ST elevation myocardial infarction, PCI, percutaneous coronary intervention.

pump. The rate of complete revascularization was 97% for female gender and 98% for male gender, respectively (*Table 2*).

At the coronary anastomosis sites of LAD (40.4% *vs.* 14.5%; P=0.0015), obtuse marginal (25% *vs.* 6.8%; P=0.0331), posterior descending (25% *vs.* 5.3%; P=0.0803)

Table 2 Anatomical and perioperative data

Variables	Women (n=162)	Men (n=882)	P value
Diameter anterior descending artery, mm	1.53±0.2	1.70±0.2	<0.0001
Diameter diagonal branch/s, mm	1.41±0.3	1.61±0.2	0.01
Diameter obtuse marginal branch/s, mm	1.48±0.3	1.70±0.2	<0.0001
Diameter right coronary art, mm	1.56±0.4	1.93±0.4	<0.001
Diameter posterior descending artery, mm	1.32±0.4	1.49±0.2	0.01
No. diseased vessel per-patient	2.6±0.5	2.7±57	0.57
Left main disease	41 [25.3]	247 [28]	0.75
Cardiopulmonary bypass, min	89.3±33	101±65	0.07
Aortic cross-clamp, min	53.5±23	58.9±34	0.11
No. grafts per-patient	2.6±0.7	2.8±0.8	0.005
L-ITA use	158 [97.5]	837 [94.9]	0.85
Off pump coronary artery bypass	11 [6.79]	74 [8.39]	0.71
Completeness of revascularization	157 [97]	864 [98]	0.87

Data are presented as mean ± standard deviation or n [%]. L-ITA, left internal thoracic artery.

Table 3 Perioperative outcomes

Variables	Women (n=162), n (%)	Men (n=882), n (%)	P value
Operative mortality	5 (3.09)	17 (1.93)	0.37
Postoperative low cardiac output syndrome with or without perioperative MI	8 (4.9)	45 (5.1)	0.86
Acute renal dysfunction	6 (3.7)	39 (4.4)	0.82
Combined end-point (the three listed above)	19 (11.7)	101 (11.5)	0.91
Respiratory failure	12 (7.4)	106 (12.0)	0.01

MI, myocardial infarction.

branches, females presented higher incidence of plaque atherosclerotic coronary disease than males. Males had, on the contrary, showed higher incidence of calcific (31% *vs.* 30%; 19.3% *vs.* 13.6%; 35.7% *vs.* 33%) and fibro-sclerotic (13.6% *vs.* 7%; 5.6% *vs.* 4.5%; 7.1% *vs.* 4.2%) disease, or preserved arterial wall (41% *vs.* 23%; 68% *vs.* 57%; 52% *vs.* 38%).

Operative mortality was 2.11% in the whole population (22/1,044): 3.09% (5/162) in female sex and 1.93% (17/882) in male sex (P=0.37). The incidence of postoperative complications analyzed were similar in the two groups of patients with the exception of primary respiratory failure, which was greater in men. Considering the combined endpoint of hospital death, low cardiac output syndrome, and worsening renal failure, the overall incidence was 11.7% (19/162) in females *vs.* 11.5% (101/882) in males (*Table 3*).

Independent predictors of operative mortality were emergency CABG (P<0.0001), previous PCI urgently performed within 30 days before CABG (P=0.0026), and the high-risk (H) EuroSCORE II (P=0.0155) (*Table 4*).

Medical therapy at discharge was the same for both females and males, and consisted for a period of 1–2 months in the administration of acetylsalicylic acid (ASA) 100 mg per day, beta-blockers 1.25-2.5-5.0 mg per day, statins 40 to 80 mg per day, anti-hypertensive drugs. Diuretic therapy with furosemide 25 to 50 mg per day, and potassium-sparing diuretic 25 to 100 mg was discontinued after

Table 4 Risk factors and independent predictors of operative mortality

Variables	P value (univariate)	Hazard ratio	95% CI	P value (multivariable)
Emergency *vs.* urgent and elective CABG	<0.0001	20.9	4.72–93.2	<0.0001
PCI within 30 days before CABG	0.0011	0.13	0.02–0.78	0.0026
EuroSCORE, H group *vs.* M and L groups	<0.0001	7.13	1.45–35.0	0.0155
Previous PCI	0.0683	0.32	0.09–1.15	0.0795
Severe chronic renal dysfunction	0.0003	0.37	0.10–1.37	0.1383
Recent MI (at 30 days)	0.0236	0.73	0.22–2.46	0.6130
Age at operation	0.0036	0.99	0.93–1.06	0.8780
LVEF (0.48 *vs.* 0.53)	0.0001	1.02	0.96–1.09	0.4855
Female gender	0.3456	–	–	–

CI, confidence interval; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; H, high, M, medium; L, low; MI, myocardial infarction; LVEF, left ventricular ejection fraction.

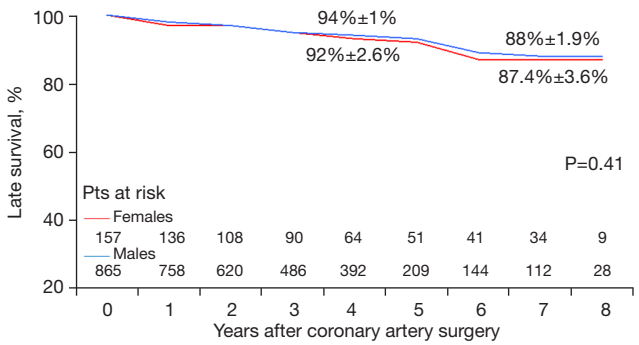

Figure 1 Mid-term survival in female and male gender after CABG [mean follow-up, 40±27 (median 38) months]. The percentage estimates reported refer to 4 and 7.5 years of follow-up, respectively. CABG, coronary artery bypass grafting.

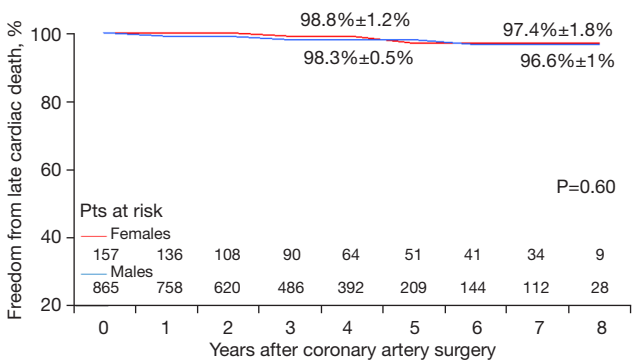

Figure 2 Freedom from late cardiac death in female and male gender after CABG. The percentage estimates reported refer to 4 and 7.5 years of follow-up, respectively. CABG, coronary artery bypass grafting.

one month. Clopidogrel 75 mg per day in association with ASA (double anti-aggregation therapy) was maintained in the presence of CABG operations performed for acute coronary syndromes, and in any case re-evaluated by the cardiologist during the follow-up. During the follow-up, except for specific contraindications, all patients were on triple therapy based on ASA 100 mg per day, beta-blockers and statin, in association, if necessary, with antihypertensive drugs, i.e., ace-inhibitors and sartanic drugs.

Late results

Follow-up was 98% complete; 19 patients were lost. At 7.5 years, actuarial survival was 87.4%±3.6% for female gender *vs.* 88%±1.9% in male gender (P=0.41) (*Figure 1*), freedom from late cardiac death 97.4%±1.8% *vs.* 96.6%±1.0% (P=0.6) (*Figure 2*), freedom from MACE 89.7%±2.5% *vs.* 87%±6.2% (P=0.96) (*Figure 3*). During follow-up, there were 58 late deaths (10 females and 48 males) out of 1,022 patients survived after coronary surgery (5.67%); 17 (2 females and 15 males) of them (29.3%) were due to cardiac causes. MACE occurred in 33 patients (3.23%) (6 females and 27 males).

Female gender was not identified as a risk factor for late death or reduced freedom from adverse cardiovascular events in both linear and multivariate Cox regression analysis.

The only independent predictor of all-causes late death (P<0.0001) and reduced freedom from cardiac death (P=0.0385) detected at the Cox regression analysis was the advanced age at the operation time (*Tables 5*,*6*).

The rank-test analyses showed a significant worse outcome in patients affected by severe chronic renal dysfunction (74%±7% *vs.* 90%±2.0%, P<0.0001), and in patients with high-risk EuroSCORE [62%±11% *vs.* 82%±5.5% (medium risk) and 93%±2.0% (low risk), P<0.0001] without highlighting statistically significant differences between gender (P>0.5, for both interactions) (*Figures 4,5*).

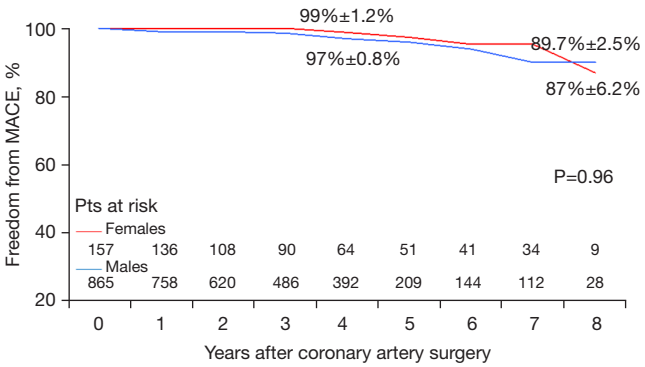

Figure 3 Freedom from MACE. The percentage estimates reported refer to 4 and 7.5 years of follow-up, respectively. MACE, major adverse cardiac event.

Discussion

The influence of the female gender on operative and late results after CABG is still a topic of debate today, after thirty years of observation. Several reasons have been reported in the literature to fully or at least partially explain a possible worse outcome of female gender after CABG. First, it is reported that there is a difference from the first time of admission to diagnostic cardiac catheterization in female gender in comparison with men, which may account, given the delay observed, for the more severe urgent or emergent clinical presentation at the time of CABG surgery, consequently increasing the operative risk in women (8). Secondly, the progression of the atherosclerotic disease most likely occurs in women at the end of childbearing age, i.e., when the protective estrogenic effect is less and therefore as compared with men, women arrive at the observation with more advanced age, which "*per se*" represents one of the most important predictors of worse in-hospital outcome (9,10). Third, it has been observed that women, having a smaller body surface area, have a smaller caliber of the coronary arteries than men, and therefore the risk of incomplete or imperfect revascularization, i.e., early graft failure, can determine worse short- and long-term outcome. Furthermore, given the technical difficulty related

Table 5 Risk factors and independent predictors of late survival

Variables	P value (Cox linear analysis)	Hazard ratio	95% CI	P value (Cox regression)
Advanced age at the operation time (74 *vs.* 67 years)	<0.0001	1.10	1.05–1.15	<0.0001
Reduced LVEF (0.49 *vs.* 0.53)	0.0081	0.97	0.93–1.00	0.0748
EuroSCORE, H risk group *vs.* M and L risk groups	0.0348	0.50	0.21–1.34	0.1797
Severe chronic renal dysfunction	<0.0001	2.05	0.91–4.64	0.0835
Female gender	0.4109	–	–	–

CI, confidence interval; LVEF, left ventricular ejection fraction; H, high, M, medium; L, low.

Table 6 Risk factors and independent predictors of late cardiac death

Variables	P value (Cox linear analysis)	Hazard ratio	95% CI	P value (Cox regression)
Advanced age at the operation time (74 *vs.* 67 years)	<0.0001	1.08	1.00–1.15	0.0385
Reduced LVEF (0.48 *vs.* 0.52)	0.0577	0.96	0.91–1.02	0.1705
EuroSCORE, H risk group *vs.* M and L risk groups	0.0628	0.72	0.15–3.49	0.1797

CI, confidence interval; LVEF, left ventricular ejection fraction; H, high, M, medium; L, low.

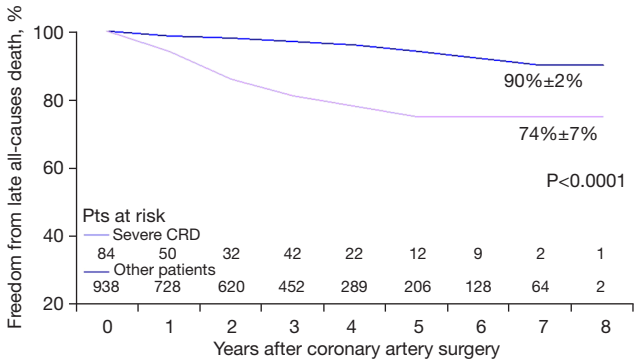

Figure 4 Mid-term survival stratified by the severe degree of CRD [Log rank, Mantel-Cox test P value <0.0001; P value for gender interaction (female *vs.* male) =0.51]. The percentage estimates reported refer to 7.5 years of follow-up. CRD, chronic renal dysfunction.

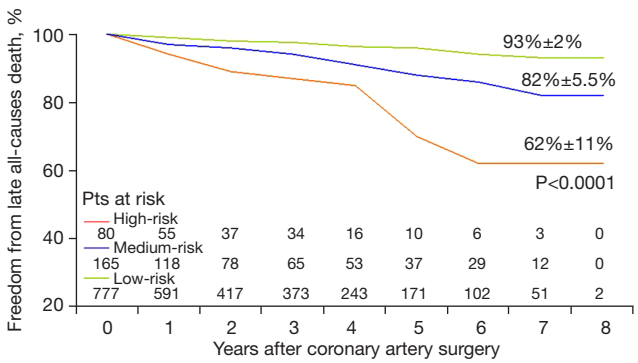

Figure 5 Mid-term survival stratified by the EuroSCORE II risk profile (low, medium, high) (Log rank, Mantel-Cox test P value <0.0001; P value for gender interaction =0.87). The percentage estimates reported refer to 7.5 years of follow-up.

with the anatomy of the coronaries, the times of the surgical intervention can be longer, thus causing an increase in postoperative serious cardiac complications, i.e., myocardial infarction and low-output syndrome (11-13).

Early results

The incidence of female gender in the population of patients undergoing CABG studied by us was 15.5% (162/1,044), and was comparable with the incidence reported in the most recent literature. Thus, it was possible to carry out an adequate analysis of the potential risks related to the female gender. Contrary to what has been reported in other studies, female gender has not been identified as a risk factor for an increase in operative mortality, neither to univariate or multivariate analysis. In fact, the operative mortality of 3.09% was slightly higher than for men (1.93%), but women had an older age at admission (+3.7 years). Even the significantly higher EuroSCORE observed in women appeared to be primarily related to their advanced age, considering that the mentioned score level increases by about one percentage point every 4.5 years of older age. For the rest, statistically significant differences in the clinical picture, i.e., stable angina and acute coronary syndromes, and on the indications for CABG, i.e., elective, urgent and emergent, were not found between the two genders. The mean number of diseased vessels per-patient as well as the incidence of significant left main disease were also comparable. The only difference was found in the higher incidence of obesity in females, but obesity was not identified as a risk factor. Even considering the combined end-point of operative death, postoperative cardiac and cardiovascular complications, we found no statistically significant difference between females and males (P>0.9). In our study, we observed only in males a higher incidence of postoperative primary respiratory insufficiency, probably related with the fact that males smoked more.

Other well-known risk factors had a decidedly more relevant weight on the increased operative mortality in our series, such as emergency CABG, a longer history of ischemic heart disease represented by percutaneous coronary revascularization performed prior to CABG, and the highest risk of EuroSCORE II (group H) (*Table 4*). Several reasons may have contributed to similar operative results in our study. Panahiazar *et al.* (8) reported that, as compared with men, women had an extra 127 days delay between angiographic diagnosis and coronary artery bypass graft. Being a referral center for CABG surgery, it is possible that there was no delay in the clinical diagnosis and surgical treatment in women in comparison with men. In fact, although we did not conduct a specific study on this aspect, clinical presentation between females and males in clinical picture, i.e., stable and unstable angina, myocardial infarction, as well as in the indication to CABG suggested no substantial differences. Some studies point out that the worst hospital outcome observed in female gender may be related to longer surgical times required to perform the anastomoses on smaller coronaries in comparison with those of men. In a study carried out on 1,325 patients, O'Connor *et al.* found an inverse relationship between the mean diameter of the LAD branch and the operative

mortality, i.e., 4.6% in presence a diameter of 1.5–2.0 mm *vs.* 1.5% for a diameter greater than 2.0 mm (14). In our population the mean value of the diameter of the three main coronary branches was significantly smaller in females in comparison with males counterpart, but the lower value of the vessel diameter found in women was not identified as risk factor of increased mortality, as previously reported (15,16). The smaller caliber of the coronary arteries in the female gender is expected, as it correlates with a smaller body surface area (14): we also observed that women were significantly shorter in comparison with men. Despite the caliber of female coronaries was smaller, the aortic clamping and cardiopulmonary times bypass were not statistically different. Indeed, aortic cross clamp and extracorporeal circulation times were a little longer in males, but this was mainly related to a higher mean number of distal and proximal anastomoses performed in males.

In summary, the similar intraoperative outcomes observed in our study could be justified by the fact that the clinical presentation in male and female gender at the time of admission was similar, without any delay for the female gender, and that surgical times and number of grafts were substantially similar in both genders.

Late results

The possible negative effect of female gender on medium- and long-term prognosis after CABG is still a matter of open debate. In some studies, it is reported that the worst long-term prognosis of women may depend on female gender "*per se*" (6-8), in other studies on the worst clinical presentation typical for females, even after CABG surgery. Nurkkala *et al.* (9) in a systematic analysis of 5,950 CABG patients (962 women, 16%) observed that the risk of cardiac death was 2.5-fold greater in women undergoing CABG than in men operated in comparison to non-operated healthy counterparts of the same sex. That is, the risk of cardiac death of women undergoing CABG is more than double that of men and it remains higher for a long-term period of follow-up. The authors attribute the excess mortality in women to their comorbid burden, lack of adequate secondary prevention to control diabetes and hypertension, and lack of adequate medical treatment even after CABG. It has also been reported that coronary artery disease in females is partly different from males, due to a greater presence of atherosclerotic plaques, which can undergo erosion or fissuring over time even after CABG, and therefore can lead to an increase in late mortality (17). Also in our study we observed intraoperatively that there was a significantly greater incidence of atherosclerotic and plaque disease in females coronary vessels in comparison with males, in which, on the contrary, a greater incidence of parietal calcifications was found. Diffuse parietal calcifications of the vessels probably may represent an indicator of more old atherosclerotic disease, but at the same time, of lower risk of sudden progression, thus associated with a better late prognosis. However, during the follow-up we did not observe significant differences in terms of survival, freedom from cardiac death and from MACE in the two sexes, at least for a medium-long term follow-up. Instead, as reported by other papers, female sex was not identified as a predictor of worse prognosis. The IMAGINE (Ischemia Management with Accupril post-bypass Graft via Inhibition of the converting Enzyme) study (18) performed on 2,553 CABG patients (324 females, 13%) showed that, after adjustment for age and confounder factors, female gender became a non-significant predictor for prognosis at 32 months after operation. In a retrospective study published by Jang *et al.* (19) on 6,613 patients undergoing CABG (1,679 females, 25.4%) during a follow-up of 54 months the incidence of cardiovascular death or myocardial infarction was not statistically different between females and males (7.5% *vs.* 5.7%, P=0.735); after propensity score matching the difference remained still not significant (P=0.666). Also in our study, Cox's linear analysis did not identify female sex as any predictor of a worse prognosis in the medium term follow-up. The advanced age at the time of surgery (+7 years; P<0.001, for both analyses) was identified as the only predictor of worse mid-term outcomes [hazard ratios (HRs): 1.1 and 1.08 for all causes death and cardiac death, respectively]. At different levels and methods of statistical analysis, i.e., linear Cox analysis and Mantel Cox log rank tests, the more depressed LV systolic function, the higher EuroSCORE II value and the severe preoperative chronic renal dysfunction have determined an important increase in late all-causes and cardiac mortality. The observed survival and freedom from late cardiac death appeared to be very and equally satisfactory in females and males. The reasons for a similar outcome could be attributable, at least in part, to some aspects related to surgical revascularization. The territory of LAD artery was always revascularized, and this factor could undoubtedly improve the long-term prognosis of the whole studied population. Even the extensive use of the internal mammary artery and the similar high rate of completeness of the revascularization may have played an important

role in obtaining the good results, also in female gender. For the territory of the left descending anterior artery the left internal thoracic artery grafting provides a long-term benefit and improvement in survival. It has been reported that long-term survival is predominantly conditioned more by a good left internal thoracic artery-anterior descending artery graft rather than by an incomplete revascularization of the other non-LAD territories (20-22). In our series, left internal thoracic artery was almost always used. In both females and males the achieved mean number of grafts per-patient was greater than 2.5, i.e., 2.6 *vs.* 2.8, indicating quite sufficient completeness of revascularization, thus likely providing a comparable satisfactory late prognosis. Indeed, freedom form cardiac death observed in both genders was very and equally satisfactory.

An important aspect that we observed in our study is that the medical therapy administered after surgery on discharge, and during the follow-up, appeared to be similar in both men and women and complete, both in terms of the prevention of cardiovascular risk factors, and for the control of the progression of atherosclerotic disease. In fact, all patients have been better followed in our clinics, and therapy administration with ASA, beta-blockers, statins, antihypertensive drugs, have been equally administered in females and in males.

In summary, the similar mid-term outcomes observed in our study may be related to a surgical strategy substantially equivalent and to a strict control of risk factors with the medical therapy after CABG similarly administered in both genders.

Limitations of the study

This study was a retrospective, non-randomized, non-propensity score matched study. Moreover, the study included patients from a single center only, and the sample of females is quite small. Another limitation was represented by the length of the follow-up, that has had a duration of a medium-long period, i.e., at 5–7 years. Therefore, it does not allow us to draw conclusions on a longer period of observation. However, we analyzed the entire consecutive patient population of females and males undergoing CABG in the last 7-year period of surgical activity, in order to obtain patient clinical information as accurate and complete as possible, and to make a sufficiently reliable statistical analysis.

Certainly, regardless of what we have observed, in most of the works published over the course of 20 years, all the authors have reported operative mortality values and long-term results, whether they had statistical significance or not, generally always worse for the female gender. These observations, regardless of the CABG operative risk, suggests that there may still be a difference in chances of the correct medical treatment in women compared to men as regards the secondary prevention of cardiovascular risk factors and, more generally, the diagnostic-therapeutic pathway, both before and after CABG. Therefore, our results should be taken with caution, because they refer to a single center and cannot be generalized.

Conclusions

From what was observed in our analysis, in spite of what is still reported today by a rather well-represented literature, as thought by our initially hypothesis of this study, women undergoing CABG with the same surgical techniques and medical therapy currently adopted for male gender, do not appear to be associated with worse prognosis. Freedom from late all-causes mortality, cardiac death and adverse cardiac events are comparable and equally satisfactory, highlighting the positive protective effect of CABG over time in both women and men. In summary, it would seem evident that by giving the same diagnostic and therapeutic chances also to the female gender before and after surgery, the results appear to be substantially similar and very satisfactory.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-932/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-932/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-932/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-932/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Tor Vergata Polyclinic (108/23 No. Protocol code, date of approval 05.05.2023). Informed consent was obtained from all subjects involved in the study.

References

1. Lundberg G, King S. Coronary revascularization in women. Clin Cardiol 2012;35:156-9.
2. Saxena A, Dinh D, Smith JA, et al. Sex differences in outcomes following isolated coronary artery bypass graft surgery in Australian patients: analysis of the Australasian Society of Cardiac and Thoracic Surgeons cardiac surgery database. Eur J Cardiothorac Surg 2012;41:755-62.
3. Lichtman JH, Leifheit EC, Safdar B, et al. Sex Differences in the Presentation and Perception of Symptoms Among Young Patients With Myocardial Infarction: Evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). Circulation 2018;137:781-90.
4. Blasberg JD, Schwartz GS, Balaram SK. The role of gender in coronary surgery. Eur J Cardiothorac Surg 2011;40:715-21.
5. Gaudino M, Di Franco A, Alexander JH, et al. Sex differences in outcomes after coronary artery bypass grafting: a pooled analysis of individual patient data. Eur Heart J 2021;43:18-28.
6. Chang FC, Chen SW, Chan YH, et al. Sex differences in risks of in-hospital and late outcomes after cardiac surgery: a nationwide population-based cohort study. BMJ Open 2022;12:e058538.
7. Gaudino M, Chadow D, Rahouma M, et al. Operative Outcomes of Women Undergoing Coronary Artery Bypass Surgery in the US, 2011 to 2020. JAMA Surg 2023;158:494-502.
8. Panahiazar M, Bishara AM, Chern Y, et al. Gender-based time discrepancy in diagnosis of coronary artery disease based on data analytics of electronic medical records. Front Cardiovasc Med 2022;9:969325.
9. Nurkkala J, Kauko A, Palmu J, et al. Sex differences in coronary artery bypass grafting-related morbidity and mortality. Front Cardiovasc Med 2022;9:1021363.
10. Shi D, Zhang B, Motamed M, et al. Higher Mortality in Women After Coronary Artery Bypass: Meta-analysis and Bias Analysis of Confounding. Ann Thorac Surg 2022;113:674-80.
11. Filardo G, Hamman BL, Pollock BD, et al. Excess short-term mortality in women after isolated coronary artery bypass graft surgery. Open Heart 2016;3:e000386.
12. Johnston A, Mesana TG, Lee DS, et al. Sex Differences in Long-Term Survival After Major Cardiac Surgery: A Population-Based Cohort Study. J Am Heart Assoc 2019;8:e013260.
13. Ram E, Sternik L, Moshkovitz Y, et al. Coronary Artery Bypass Grafting Following Acute Coronary Syndrome: Impact of Gender. Semin Thorac Cardiovasc Surg 2022;34:920-9.
14. O'Connor NJ, Morton JR, Birkmeyer JD, et al. Effect of coronary artery diameter in patients undergoing coronary bypass surgery. Northern New England Cardiovascular Disease Study Group. Circulation 1996;93:652-5.
15. Nardi P, Pellegrino A, De Paulis R, et al. Coronary heart surgery in women: the risk factors and short-term results. Ital Heart J Suppl 2000;1:537-42.
16. Russo M, Nardi P, Saitto G, et al. Single versus double antiplatelet therapy in patients undergoing coronary artery bypass grafting with coronary endarterectomy: mid-term results and clinical implications. Interact Cardiovasc Thorac Surg 2017;24:203-8.
17. Schmidt AF, Haitjema S, Sartipy U, et al. Unravelling the Difference Between Men and Women in Post-CABG Survival. Front Cardiovasc Med 2022;9:768972.
18. den Ruijter HM, Haitjema S, van der Meer MG, et al. Long-term outcome in men and women after CABG; results from the IMAGINE trial. Atherosclerosis 2015;241:284-8.
19. Jang WJ, Choi KH, Kim J, et al. Impact of gender on mid-term prognosis of patients undergoing coronary artery bypass grafting. PLoS One 2023;18:e0279030.
20. Rastan AJ, Walther T, Falk V, et al. Does reasonable

incomplete surgical revascularization affect early or long-term survival in patients with multivessel coronary artery disease receiving left internal mammary artery bypass to left anterior descending artery? Circulation 2009;120:S70-7.
21. Head SJ, Mack MJ, Holmes DR Jr, et al. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. Eur J Cardiothorac Surg 2012;41:535-41.
22. Taggart DP. Incomplete revascularization: appropriate and inappropriate. Eur J Cardiothorac Surg 2012;41:542-3.

Cite this article as: Nardi P, Pisano C, Bassano C, Bertoldo F, Buioni D, Labriola V, Salvati AC, Scognamiglio M, Altieri C, Ruvolo G. The role of the female gender on mid-term outcome after coronary artery bypass grafting: a retrospective study. J Thorac Dis 2024;16(2):862-874. doi: 10.21037/jtd-23-932